REMARKS

Entry of the foregoing and favorable reconsideration of the subject application, pursuant to and consistent with 37 C.F.R. Section 1.112, and in light of the remarks which follow, are respectfully requested.

Claim 66 has been revised so as to be placed in independent form. New claims 82 to 84 have been added. The new claims are fully supported by an enabling disclosure.

By the present amendment new Claims 71 to 73 have been added. Support for this amendment appears at least in Claims 60, 66, 68, 69 and 70, currently of record. Applicants submit that no new matter has been added via this amendment.

Claims 56-67 have been rejected under 35 U.S.C. § 102 (b) as being anticipated by Menozzi et al. (*Abstracts of the General Meeting of the ASM, 95(0):193, abstract B-159*). For the following reasons, however, this rejection is respectfully traversed.

It should be clear to be anticipatory a reference must disclose each and every element of the claim in the same order as arranged in the claim. See, *Brown v. 3M,* 265 F3d 1349, 1351, 60 USPQ2d 1375 (Fed. Cir. 2001) *cert denied*, 122 S. Ct. 1436 (2002).

The Menozzi et al Abstract cited by the Examiner in this rejection does not disclose the 30 to 50 amino acids of a C-terminal portion of SEQ ID No. 19, a variant thereof or part of the last 50 amino acids of SEQ ID No. 19, wherein said variant is obtained by addition, substitution or deletion of one or more amino acids. Nor does Menozzi et al disclose the antigen of SEQ ID No.1, nor the monoclonal antibodies 4057D2 and 3921E4.

Menozzi et al fail to describe a recombinant peptide sequence which is obtainable by expression in a host cell of SEQ ID No. 19, an immunogenic composition that has the antigen of claim 56, a reactant for detecting an anti-HBHA antibody nor a kit.

Rather Menozzi et al disclose to the skilled artisan that there is a 28 kD protein derived from BCG that is a heparin-binding Hemagglutinin protein (hereinafter HBHA) purified using heparin-Sepharose chromatography from whole cell extracts, cell wall preparations and culture supernatants. Some fingerprint characteristics of this protein were described such as that this protein agglutinated erythrocytes and was inhibited by sulfated polysaccharides, but not by non-sulfated sugars. There is simply no structural characterization of this protein, but only functional characterizations.

Menozzi et al fail to disclose any procedure concerning the cloning of the gene coding for HBHA and what microorganisms can be used to express it.

It appears that the Examiner is maintaining that once a protein is purified it is well within the skill of the person in the art to clone and sequence the protein using methods known in the art. However, Applicants submit that due to the unpredictability in this art and the hundreds of choices available to clone and express this protein, without further guidance as to which of the hundreds of paths to choose from, the skilled artisan would encounter undue experimentation without any expectation of success from the mere teachings of Menozzi et al of how to purify a 28 kDA HBHA protein.

For example, what cloning vector would be appropriate from those known among those skilled in the art at the time of the filing of this application in 1996? What microorganisms could be used to express the HBHA protein? Under what experimental conditions would all of the experiments be conducted? These facts were not available from the disclosure of Menozzi et al.

The Examiner also relies on the inherency doctrine and seems to conclude that the amino acid sequences, as presently claimed, the recombinant proteins and the monoclonal antibodies are inherent in the teachings of Menozzi et al. However, Applicants submit that to maintain a novelty rejection based on inherency recognition of the claimed subject matter by the skilled artisan must be available from the disclosure of the reference. Thus, in *Cont'l Can Co. v. Monsanto Co.*, 948 F2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) the court clearly stated:

> Under the doctrine of inherency, if an element is not expressly disclosed in a prior art reference, the reference will still be deemed to anticipate a subsequent claim if the missing element "is necessarily present in the thing described in the reference, and **that it would be so recognized by persons of ordinary skill**" (emphasis added).

However, Applicants submit that the person skilled in the art could not envision the particular amino acid sequences as presently claimed, since these sequences are a particular chemical structure that of itself cannot be predicted by a purified protein present in a test tube.Moreover, the sequence that is claimed is the C-terminal part of the HBHA, which is the region involved in the heparin binding site. The identification of this particular binding site within the 28 kDA protein was not disclosed in Menozzi et al nor was a procedure to identify such site.

Thus, the disclosure in Menozzi et al does not provide within its four corners sufficient guidance on how to obtain the presently claimed invention. Applicants urge that this reference merely discloses a starting point for future undue experimentation, which starting point is not enough to anticipate the presently claimed invention.

Finally it can be said that Menozzi et al is not enabling in that there is no description of any probes that can be used to clone the gene coding for HBHA, of any expression vectors and of any microorganisms in which the protein can be expressed. Finally there is simply no guidance in Menozzi et al of how to identify the heparin binding site of HBHA and where this binding site is located on the HBHA sequence. The additional experiments set forth at least on pages 20 to 23 of the present specification, required additional ingenuity that was not apparent from the prior art teaching of Menozzi et al.

Submitted herewith is a Declaration executed by one of the inventors, Dr. Menozzi. This Declaration emphasizes that from the teachings of Abstract B-159, it would be impossible for the skilled artisan to map or even localize the heparin binding site within the HBHA protein. Additional experimentation was needed as set forth in the specification and that the monoclonal antibodies used to characterize the 28 kDA protein were not disclosed in Abstract B-159. Hence, the fact that the 28 kDA protein

was called an HBHA protein, the fact that it was present in *Mycobacterium tuberculosis* and it was surface associated and the fact that this protein was different from the 85 complex were characteristics that could not be done by the skilled artisan without knowledge of the monoclonal antibody that was used in Abstract B-159.

Hence it can only be concluded that Abstract B-159 was not enabling.

In conclusion, Applicants submit that the prior art of Menozzi et al simply cannot in any respect be novelty destroying for any of the claims of the present invention.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

From the foregoing, favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

Respectfully submitted,

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PATENT
Attorney Docket No.3.0-008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Menozzi et al.

Serial No.:09/192,579

Filed: November 17, 1998

Group Art Unit: 1645

Examiner: R. Swartz

For: IDENTIFICATION AND CLONING OF A MYCOBACTERIAL ANTIGEN CORRESPONDING TO A HEPARIN-BINDING HAEMAGGLUTININ

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

I, Franco Dante Menozzi, do hereby state and declare the following:

1. I am a co-inventor of the subject matter disclosed and claimed in the above-captioned application. I received a Doctorate in Biological Sciences from the University of Mons-Hainaut, Belgium in 1987 and am currently working at the Institut Pasteur of Lille in Lille, France. I have been a member of the American Society for Microbiology from 1991 to 2003. My Curriculum Vitae is attached as Exhibit 1.

2. I have reviewed the latest U.S. Official Action mailed December 11, 2003. It appears to me that in this Official Action the Examiner deems that the above-captioned patent application is anticipated by Menozzi et al. *Abstracts of the General Meeting of the ASM* 95(0):193, Abstract B-159. I have also reviewed the current claims in this application which recite the specific heparin binding site of HBHA and which encompass 30 to 50 amino acids of the C-terminal portion of SEQ ID No. 19 (Figure 10 in the application). It is my opinion that there was insufficient information

set forth in this Abstract for a skilled scientist to identify the heparin binding site of HBHA from the disclosure therein for the following reasons.

3. From the observations disclosed in Abstract B-159 it is my opinion that it would be impossible for the skilled scientist to map or even localize the heparin-binding site within the HBHA protein. Such a mapping required the cloning of the HBHA-encoding gene, as well as the development of biological assays based on the capability of native or recombinant HBHA fragments to interact with heparin or related sulphated polysaccharides. These assays are not described nor mentioned in Abstract B-159 and as a consequence no pertinent information or investigative strategy was given to the skilled artisan that could lead to the mapping of the HBHA heparin-binding site.

4. Even if a scientist could in fact clone and express the HBHA gene at that epoch, the identification of the heparin binding site could only be achieved by producing the recombinant form of HBHA in *E. coli* and with further analysis of the expression product. As set forth on pages 20 to 23 of the specification, several additional experiments were performed which led us to identify the heparin binding site in HBHA. These additional analysis included lysing the HBHA produced in *E. coli* and analysis of the apparent molecular weight protein, which was recombinantly produced, further chromagraphic analysis on heparin-sepharose of a clarified sonicate of *E. coli* producing the recombinant HBHA, analysis of recombinant HBHA by immobilised heparin matrix chromatography, microsequencing the 26 kDA and 25 kDA degradation products of the complete 27 kDA recombinant protein and analyzing the results obtained. None of this information is disclosed in Abstract B-159.

5. In addition mapping of the HBHA heparin-binding site required inventive ingenuity since any conclusion concerning such a mapping could not be drawn without knowing that:

(1) HBHA migrates in an aberrant fashion in a SDS-polyacrylamide gel electrophoretic analysis; and

(2) the adhesion is prone to proteolysis.

These two important features of HBHA have been demonstrated following recombinant expression of HBHA in *E. coli* and microsequencing of the peptides eluted from the heparin-sepharose column, respectively.

6. Furthermore, it should be noted that the experiments performed in paragraph 4 above, it was essential to use the monoclonal antibody 3921E4 in the analysis. This antibody is not described in Abstract B-159. Nor is the other monoclonal antibody 4057D2, used in the experimental expression section of the above-captioned patent application described in Abstract B-159. These monoclonal antibodies were crucial to the analysis of the results. For instance, the fact that the protein was present in *Mycobacterium tuberculosis* and it was surface associated could only be ascertained by using the antibodies 4057D2 and 3921E4, which were not described in Abstract B-159. Moreover, the fact that this isolated protein was called HBHA was known using the 4057 D2 antibody. Using the same 4057 D2 antibody it was known that this isolated 28 kDA protein was different from the antigen 85 complex. Therefore, there is no information in Abstract B-159 that would allow a skilled scientist to study structurally or functionally HBHA using known specific immunological reagents.

7. Therefore, in conclusion it is my belief that a scientist faced with the disclosure in Abstract B-159 could not, without additional information and guidance as given in the present specification, obtain the amino acid sequences of the heparin binding site of HBHA.

8. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

1st March 2004

Date

Franco Dante Menozzi